Original Article

Efficacy and Safety of Sofosbuvir-based Regimens in Hepatitis C Patients With Decompensated Cirrhosis: A Systematic Review and Meta-analysis

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Abstract

Background and Aims: Decompensated cirrhotic patients with hepatitis C (HCV) are often under-represented in clinical trials. We aimed to evaluate pooled data on the efficacy and safety of sofosbuvir (SOF)-based regimens in these patients. ***Methods:*** We conducted a systemic review and meta-analysis by searching multiple databases for studies published from October 2010 to October 2020. Outcomes of interest were sustained virologic response (SVR) and safety of SOF-based regimens in decompensated HCV patients. Two reviewers independently performed the study selection and data extraction. ***Results:*** We included 33 studies that enrolled 5,302 HCV patients. The pooled SVR rate in decompensated patients with SOF-based regimens was 85.1% (95% CI: 82.8–87.3). Patients on SOF/velpatasvir±ribavirin achieved a significantly higher SVR (91.0%, 95% CI: 87.7–93.9) than that of SOF/ledipasvir±ribavirin [(86.3%, 95% CI: 84.6–87.8); *p*=0.004)], or on SOF/daclatasvir±ribavirin (82.4%, 95% CI: 78.2–86.2%; *p*<0.001). Adding ribavirin to SOF-based regimens (pooled SVR 84.9%, 95% CI: 81.7–87.9) did not significantly increase the SVR [(83.8% (95% CI: 76.8–89.8%; *p*=0.76)] in decompensated patients, which was also true in subgroup analyses for each regimen within the same treatment duration. However, adding ribavirin significantly increased the frequency of adverse events from 52.9% (95% CI: 28.0–77.1) to 89.2% (95% CI: 68.1–99.9) and frequency of severe events. The pooled incidence of hepatocellular carcinoma and case-fatality of decompensated patients were 3.1% (95% CI: 1.5–5.0) and 4.6% (95% CI: 3.1–6.3), respectively. The overall heterogeneity was high. There was no publication bias. ***Conclusions:*** The analysis found that 12 weeks of SOF/velpatasvir without ribavirin is the preferred therapy, with a significantly higher SVR compared with other SOF-based regimens in decompensated HCV patients.

Introduction

The main cause of chronic liver disease is hepatitis C virus infection, with significant morbidity and mortality.[1] Messina *et al*.[2] observed that the disease burden based on seroprevalence had increased globally in the last 15 years. About 700,000 people die each year from complications associated with chronic hepatitis C infection that can lead to fibrosis, cirrhosis, and hepatocellular carcinoma (HCC).[3,4] As interferon-based regimens are not suitable for patients with decompensated liver cirrhosis because safety concerns, the new generation of direct-acting antiviral (DAA) agents including sofosbuvir (SOF), ledipasvir (LDV), and daclatasvir (DCV) offer new hope for this special population.[5] Achieving a sustained virologic response (SVR) is the current goal of the treatment of patients with HCV, defined as the inability to detect HCV RNA in plasma or serum by sensitive molecular testing after 12 (SVR12) or 24 (SVR24) weeks of treatment.[6] High SVR rates and the favorable safety profile of DAA therapy in HCV patients with compensated cirrhosis have led to widespread recommendation of DAA treatment in HCV patients with decompensated disease, particularly those on transplant waiting lists and with relatively low Model For End-Stage Liver Disease scores.[7–10]

Guidelines of professional groups including the American Association for the Study of Liver Diseases (AASLD), Infectious Diseases Society of America (IDSA), and the European Association for the Study of the Liver (EASL) recommend the use of sofosbuvir (SOF)-based DAA regimens for HCV patients with liver decompensation. These therapies include the use of SOF and velpatasvir (VEL), ledipasvir (LDV), or daclatasvir (DCV) plus ribavirin (RBV). Health care providers

should take the HCV genotype in the individual patient into consideration when selecting the regimen.[6,11] Because of serious concerns associated with drug concentrations and the related risk of toxicity in patients with decompensation, DAA regimens containing protease inhibitors (e.g. grazoprevir, voxilaprevir, or glecaprevir) should be avoided in Child-Pugh B or C patients with decompensated cirrhosis.[12] However, data on the comparison of the three aforementioned SOF-based regimens that would assist in selecting individualized treatment for such patients are limited. As SOF/VEL, is a pan-genotypic regimen that can be used to treat patients who have a genotype indication for SOF/LDV or SOF/DCV, comparison of the efficacy and safety of those regimens are needed to guide treatment decisions. Several recent cohort studies and randomized controlled trials (RCTs) of SOF-based DAA therapy without ribavirin have included HCV patients with decompensated liver disease. There is growing interest in investigating whether ribavirin can be removed from the regimens in this special population because of the high frequency of adverse events (AEs).[13] However, data from individual studies is limited. With that in mind, we designed a meta-analysis to analyze pooled outcomes on the efficacy and safety of SOF-based regimens for HCV patients with decompensated cirrhosis. We compared the SVR and AEs of the regimens and assessed the pooled SVR benefits and AEs when adding ribavirin to the DAA treatment in the patients.

Methods

Our systematic review and meta-analysis followed a protocol developed by authors CP, HBY, and JZ and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[14] The search strategy, eligibility criteria, and outcomes were registered on the PROSPERO website (CRD42020149072).

Eligibility criteria

The current review included controlled or comparative studies that enrolled HCV patients with decompensated cirrhosis, which was defined with Child-Pugh scores ≥7 points, or ascites, hepatic encephalopathy, upper gastrointestinal hemorrhage in the combination of fibrosis stage 4 within 6 months before the start of DAAs treatment. Additional eligibility criteria included: (1) study patients who had received SOF-based DAA regimens and reported outcomes that included SVR, treatment-associated AEs, and the incidence of HCC, death, and liver transplantation; (2) journal articles and meeting abstracts published in English and other languages; (3) inclusion of at least 20 adult patients ≥18 years of age.

We excluded studies that met one of the following criteria: (1) enrollment of patients who received protease inhibitors; (2) treatment with only SOF or SOF combined with ribavirin; (3) inclusion of >5% of patients with coinfection of another hepatitis virus such as hepatitis B, delta or HCC, 4) lack of measurement of SVR; (5) *in vitro* or animal studies; and 6) lack of reported safety data. If two or more studies included the same cohort of patients, the most recent one was selected for review to avoid the analyses of the duplicated data.

Search strategy

We comprehensively and systematically searched PubMed, the Cochrane Central Register of Controlled Trials, Embase, MEDLINE, and Web of Science without language restrictions from October 2010, which is the time of the first publications on SOF DAA treatment to October 2020. The search terms were "liver cirrhosis" and "Child's C, or Child C, or decompensated, or Child-Pugh C" and "Hepatic cirrhosis, or cirrhosis, or liver," and "sofosbuvir." Supplementary Table 1 summarizes the search strategy for PubMed and the other databases. We also looked at the reference lists for relevant abstracts and original research articles.

Study selection and data extraction

Two reviewers independently reviewed the titles and abstracts of the retrieved articles. Articles were selected for data extraction following review of the full text publications. Disagreements were reconciled by the consensus of the corresponding authors. For each article, two reviewers independently extracted data in duplicate using a pretested and standardized form. A third reviewer compared the content and discrepancies of the extracted data. The corresponding authors resolved inconsistencies by reviewing the full text of the articles. The extracted data were the name of first author, study type, year of publication, study country, study design, patient clinical characteristics: age, sex, body mass index, care setting, HCV RNA level, and renal function status), the severity of liver disease (Child-Pugh A/B/C), history of previous treatment for hepatitis C (treatment-naïve vs. treatment-experienced), reasons for liver transplantation before antiviral therapy (HCC non-LT vs. HCC/LT), HCV genotype, DAA regimen and treatment duration, efficacy, and safety outcomes. If the missing data in the article was not housekeeper data, we ignored it.

Assessment of outcomes

Our interests in outcomes included the treatment efficacy of SOF-based regimens assessed by SVR at 12 or 24 weeks after completion of treatment; the safety outcomes such as the frequency and percentage of AEs determined by the percentage of patients who had AEs that occurred after receiving treatment, particularly severe adverse events (SAEs) such as death, life-threatening conditions, permanent or severe disability that resulted in the patient being hospitalized, requiring extended hospital stay, or developing HCC.

Assessment of the study quality and risk of bias

Two reviewers independently evaluated the quality of each study. The risk of publication bias in randomized studies was evaluated using tools from the Cochrane Collaboration.[15] In each domain, studies was classified as having "low risk," "unclear risk," or "high risk" of bias. The risk of bias for observational studies was assessed using the modified Newcastle-Ottawa scale (NOS),[16] which includes three dimensions: participant selection (maximum 4 points), comparability (maximum 2 points), and exposure or outcomes of study participants (maximum 3 points); Based on overall scores, studies were classified as high (≥7), fair (4–6), or low quality (≤4).

Statistical analysis

We performed a meta-analysis of the data using the meta and forest plot packages in R Statistics (3.6.1). The pooled SVR12 data were analyzed for efficacy outcomes. Subgroup meta-analyses of SVR12 were performed with stratification
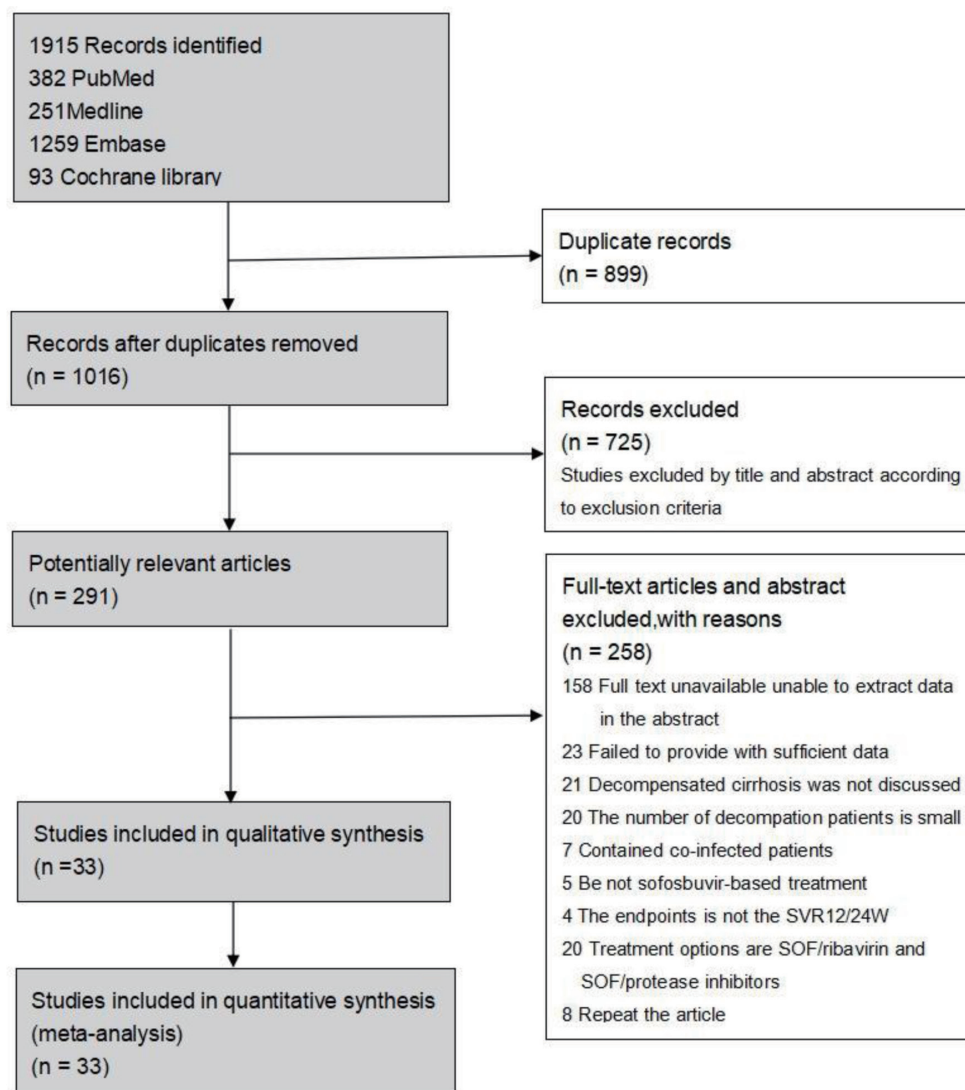
Fig. 1. Flow diagram of study selection.

by treatment regimen, HCV genotype, treatment duration, treatment location, and decompensated liver cirrhosis. As the SVR rates in the majority of studies approached 100%, we performed a Freeman-Tukey double arcsine transformation of the combined values to stabilize the variance.[17] Meta-regression was used to find difference in SVR rates between the two subgroups, and 95% confidence intervals (CIs) were calculated. The output the of meta-regression was back-transformed, and the difference between the intercept and estimate of the relevant variable was calculated. Safety data were pooled, and the analysis included the AEs, SAEs, HCC, and case-fatality rates. We then calculated the weighted difference and the pooled effect size using random-effect or fixed-effect models. To measure the overall heterogeneity across the included studies, we used the Cochrane Q test and I^2 statistic, where an I^2 value >50% or a Cochrane Q test p-value of <0.1 indicated significant heterogeneity. If heterogeneity was high, the random-effect model was used, otherwise a fixed-effect model was used. We used sensitivity analysis to explore the impact of individual studies on the overall results, deleting each study in turn to observe and evaluate whether

the results of the remaining studies differed significantly. Publication bias was assessed by Egger's Regression asymmetry test and funnel plots, with $p<0.05$ considered statistically significant.

Results

A total of 1,915 studies were identified in the initial search of the electronic databases. Of those, 33 articles met the inclusion criteria; the others were excluded. Sixteen were prospective cohort studies, nine were RCTs, and eight were retrospective analyses. Figure 1 shows the selection process and reasons for exclusion.

Study characteristics

A total of 6,976 adult patients with HCV-related cirrhosis were enrolled in our meta-analysis. The characteristics of the included studies are summarized in Table 1.[18–50] Studies

Table 1. Characteristics of the included studies

Author	Year	Study	Country	design	age	Sex Male (%)	Regimen	Duration	Genotype	SVR12/24 (DC) n/N	SVR12/24 (CC) n/N	DC/ALL (%)
Takehara[18]	2019	RCT	Japan	prospective	66 (42, 83)	39 (38)	SOF+VEL±RBV	12 weeks	1, 2, 3	94/102	–	100
Ridruejo[19]	2019	NO-RCT	Argentina, Brazil	prospective	60±12	–	SOF+DCV±RBV	12/24 weeks	1, 2, 3, 4	82/91	466/486	10
Pellicelli[20]	2019	NO-RCT	Rome, Italy	retrospective	52.6±7.9	–	SOF/DCV±RBV	24 weeks	3	23/28	199/205	12
Sanai[21]	2018	NO-RCT	Saudi Arabia	prospective	61.1±10.9	30 (63)	SOF/LDV; SOF/LDV±RBV	12/24 weeks	4	43/48	–	22.5
Garg[22]	2018	NO-RCT	India	prospective	47.2±11.51	–	SOF+LDV±RBV; SOF+DCV±RBV	12/24 weeks	1, 3	30/41	33/36	38
Young[23]	2017	NO-RCT	European	retrospective	56	–	SOF+DCV±RBV	24 weeks	1, 3, other	126/148	93/94	59.4
Hezode[24]	2017	NO-RCT	French	prospective	54.3 (34–76)	–	SOF+DCV±RBV	24 weeks	3	23/43	–	9.3
Goel[25]	2017	NO-RCT	Indian	prospective	45 (18–75)	–	SOF+DCV±RBV	24 weeks	3	18/22	28/30	18.8
Fox[26]	2017	NO-RCT	US	retrospective	–	–	SOF+LDV±RBV	8/12 weeks	1	1,133/1,299	–	21.5
Dalgard[27]	2017	NO-RCT	Scandinavia	retrospective	54	–	SOF+LDV+RBV; SOF+DCV±RBV	12–24 weeks	3	20/24	103/110	12.7
Alonso[28]	2017	NO-RCT	Spain	retrospective	55 (8)	–	SOF+DCV±RBV; SOF+LDV±RBV	12/24 weeks	3	38/42	157/166	20.2
Poordad[29]	2016	NO-RCT	Spain	prospective	58 (19–75)	–	SOF+DCV±RBV	12 weeks	1, 2, 3, 4	39/48	–	42.5
Foster[30]	2016	NO-RCT	UK	prospective	54 (28–79)	297 (73)	SOF+DCV±RBV; SOF+LDV±RBV	12 weeks	1, 3, other	329/409	–	87.6
Cheung[31]	2016	NO-RCT	England	prospective	54 (28–79)	–	SOF+DCV±RBV; SOF+LDV±RBV	12 weeks	1, 3, other	317/406	–	82.8
Backus[32]	2016	NO-RCT	US	prospective	61.66±6.0	–	SOF+LDV±RBV	8/12 weeks	1	117/133	–	3.0
Abaalkhail[33]	2016	NO-RCT	Middle East	prospective	59.5	13 (54)	SOF+LDV±RBV	12/24 weeks	4	20/24	36/37	21.6
Leroy[34]	2016	NO-RCT	France	prospective	55	–	SOF+DCV±RBV	24 weeks	–	78/93	–	100
Petersen[35]	2016	NO-RCT	European	prospective	–	–	SOF+DCV±RBV	24 weeks	1a, 1b, 3	123/147	–	100
Flamm[36]	2019	NO-RCT	France, USA	prospective	55 (39–77)	26 (81)	SOF+VEL+RBV	12 weeks	1, 2, 3, other	25/32	–	100

(continued)

Table 1. *(continued)*

Author	Year	Study	Country	design	age	Sex Male (%)	Regimen	Duration	Genotype	SVR12/24 (DC) n/N	SVR12/24 (CC) n/N	DC/ALL (%)
Zhang[37]	2019	NO-RCT	Cambodian	retrospective	59 (55–65)	41 (38)	SOF+DCV±RBV	12/24 weeks	–	89/107	–	100
El-Sherif[38]	2018	RCT	US	prospective	59 (54–62)	–	SOF+LDV+RBV; SOF+VEL±RBV	12/24 weeks	1, 2, 3, 4	509/594	–	100
Abd Alla[39]	2018	RCT	Egypt	prospective	19–72	–	SOF+LDV	24 weeks	4	42/50	25/25	66.7
Welzel[40]	2016	RCT	Germany	prospective	57.0 (27–87)	–	SOF+DCV±RBV	24 weeks	1, 2, 3, 4, 5	131/165	200/223	34
Manns[41]	2016	RCT	Germany	prospective	58 (54–62)	113 (68)	SOF+LDV+RBV	12 weeks	1, 4	131/160	65/67	47.9
Curry[42]	2015	RCT	USA	prospective	58 (43–72)	186 (70)	SOF+VEL±RBV	12 weeks	1, 2, 3, 4, 6	234/267	–	100
Troland[43]	2017	RCT	Greater Glasgow	prospective	49.4 (7.1)	–	SOF+DCV+RBV	12 weeks	3	21/25	24/26	43.1
Bansal[44]	2017	RCT	India	prospective	50 (35–70)	–	SOF+DCV+RBV	24 weeks	–	31/32	42/42	17.2
Liu[45]	2018	RCT	China	prospective	60 (27–85)	–	SOF+LDV±RBV; SOF+DCV±RBV; SOF+VEL±RBV	12/24 weeks	1, 2, 3, 4, 6	39/43	118/127	8.3
Atsukawa[46]	2020	NO-RCT	Japan	prospective	65 (43–86)	38 (59)	SOF+VEL	12 weeks	1, 2	61/64	–	100
Gheorghe[47]	2020	NO-RCT	Romania	retrospective	61 (35–83)	–	SOF+LDV±RBV	12/24 weeks	1b	174/209	123/140	100
Tahata[48]	2020	NO-RCT	Japan	prospective	68 (40–87)	43 (52)	SOF+VEL	12 weeks	1, 2, 3	74/82	–	42.2
Takaoka[49]	2020	NO-RCT	Japan	retrospective	68 (62–72)	39 (54)	SOF+VEL	12 weeks	1, 2	69/72	–	100
Zhang[50]	2020	NO-RCT	Cambodia	prospective	60.2 (55.5–65.8)	–	SOF+DCV	12/24 weeks	1, 2, 6	175/264	2,235/2,494	2.9

N, total number of patients included in the study; *n*, number of patients with sustained viral response at 12/24 weeks after the end of treatment. DC, decompensated cirrhosis; SOF, sofosbuvir; LDV, ledipasvir; VEL, velpatasvir; DCV, daclatasvir; RBV, ribavirin; RCT, random effects model.
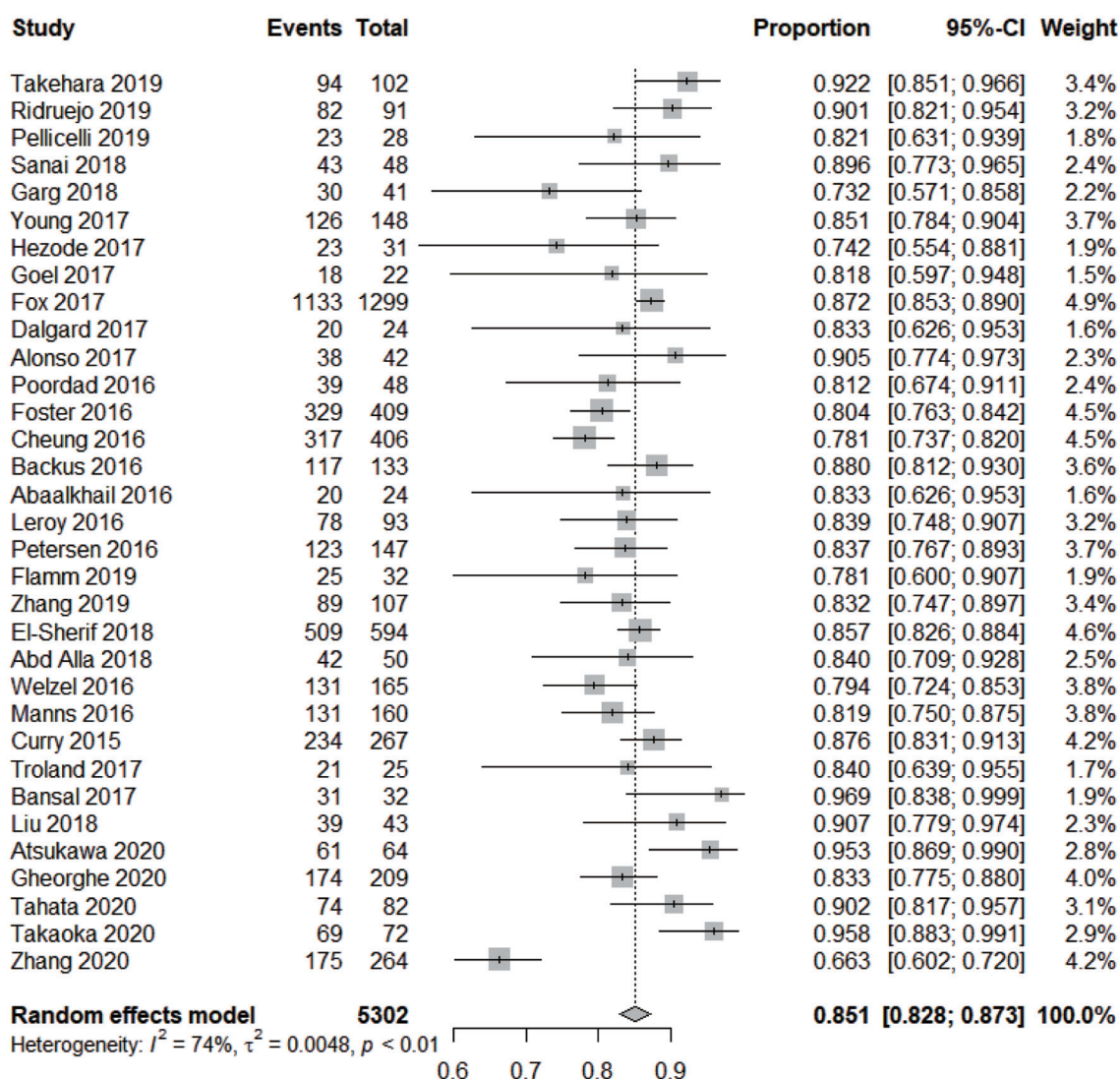
Study	Events	Total	Proportion	95%-CI	Weight
Takehara 2019	94	102	0.922	[0.851; 0.966]	3.4%
Ridruejo 2019	82	91	0.901	[0.821; 0.954]	3.2%
Pellicelli 2019	23	28	0.821	[0.631; 0.939]	1.8%
Sanai 2018	43	48	0.896	[0.773; 0.965]	2.4%
Garg 2018	30	41	0.732	[0.571; 0.858]	2.2%
Young 2017	126	148	0.851	[0.784; 0.904]	3.7%
Hezode 2017	23	31	0.742	[0.554; 0.881]	1.9%
Goel 2017	18	22	0.818	[0.597; 0.948]	1.5%
Fox 2017	1133	1299	0.872	[0.853; 0.890]	4.9%
Dalgard 2017	20	24	0.833	[0.626; 0.953]	1.6%
Alonso 2017	38	42	0.905	[0.774; 0.973]	2.3%
Poordad 2016	39	48	0.812	[0.674; 0.911]	2.4%
Foster 2016	329	409	0.804	[0.763; 0.842]	4.5%
Cheung 2016	317	406	0.781	[0.737; 0.820]	4.5%
Backus 2016	117	133	0.880	[0.812; 0.930]	3.6%
Abaalkhail 2016	20	24	0.833	[0.626; 0.953]	1.6%
Leroy 2016	78	93	0.839	[0.748; 0.907]	3.2%
Petersen 2016	123	147	0.837	[0.767; 0.893]	3.7%
Flamm 2019	25	32	0.781	[0.600; 0.907]	1.9%
Zhang 2019	89	107	0.832	[0.747; 0.897]	3.4%
El-Sherif 2018	509	594	0.857	[0.826; 0.884]	4.6%
Abd Alla 2018	42	50	0.840	[0.709; 0.928]	2.5%
Welzel 2016	131	165	0.794	[0.724; 0.853]	3.8%
Manns 2016	131	160	0.819	[0.750; 0.875]	3.8%
Curry 2015	234	267	0.876	[0.831; 0.913]	4.2%
Troland 2017	21	25	0.840	[0.639; 0.955]	1.7%
Bansal 2017	31	32	0.969	[0.838; 0.999]	1.9%
Liu 2018	39	43	0.907	[0.779; 0.974]	2.3%
Atsukawa 2020	61	64	0.953	[0.869; 0.990]	2.8%
Gheorghe 2020	174	209	0.833	[0.775; 0.880]	4.0%
Tahata 2020	74	82	0.902	[0.817; 0.957]	3.1%
Takaoka 2020	69	72	0.958	[0.883; 0.991]	2.9%
Zhang 2020	175	264	0.663	[0.602; 0.720]	4.2%
Random effects model		**5302**	**0.851**	**[0.828; 0.873]**	**100.0%**

Heterogeneity: $I^2 = 74\%$, $\tau^2 = 0.0048$, $p < 0.01$

0.6 0.7 0.8 0.9

Fig. 2. Forest plots of SVR12 rates of all hepatitis C patients with cirrhosis. The dotted vertical line and the diamond show the summary effect (random-effect model); outer edges show the 95% confidence intervals (CIs). SVR, sustained virologic response.

published from 2015 to 2020 included 5,302 HCV patients with decompensated and 1,674 with compensated cirrhosis. However, the enrollment of study patients in those studies could have been before 2015. The majority of patients were Caucasian. The treatment regimens were SOF/VEL, SOF/LDV, and SOF/DCL for t 12 to 24 weeks. Ribavirin was added to the regimens in 28 studies. All RCTs were considered to be high quality studies based on the methods of randomization and allocation concealment, and were found to have low risk of bias in terms of attrition, outcome reporting, and detection. Of 24 nonrandomized cohort studies, 22 had NOS scores ≥7 and were considered to be of high quality. The remaining two studies were of medium quality with scores of 4–6 points. Comprehensive evaluation of the risk of bias is shown in Supplementary Table 2.

Overall treatment outcomes of patients with decompensated cirrhosis

The treatment of cirrhotic patients with HCV with the afore-

mentioned DAA regimens yielded high cure rates. The pooled SVR12 rate for all 5,302 patients with decompensated hepatitis C cirrhosis in the 33 studies was 85.1% (95% CI: 82.8–87.3). The random-effect model was used in the analysis because the I^2=74% (χ^2=0.0048, $p<0.01$). The forest plots of SVR12 rates are shown in Figure 2. For comparison of pooled SVR rates in HCV patients with cirrhosis at the compensated versus decompensated stages, we compiled the SVR data from 14 studies including 1,674 patients with compensated cirrhosis and 5,302 with decompensated cirrhosis (Fig. 3). A significantly higher pooled SVR rate was found in the compensated group [95.8% (95% CI: 94.0–97.3) vs. 85.1% (95% CI: 82.8–87.3); $p<0.001$] (Supplementary Fig. 1). In a meta-regression model, the pooled SVR rate of patients with decompensated cirrhosis treated with DAA was 10.1% (95% CI: 6.6–13.6) lower than that of patients with compensated cirrhosis.

When we analyzed the two groups following stratification by DAA regimen (Fig. 3, Supplementary Table 3), The pooled SVR rates remained significantly lower in the decompensated patients who received SOF/LDV±RBV [86.6% (95%
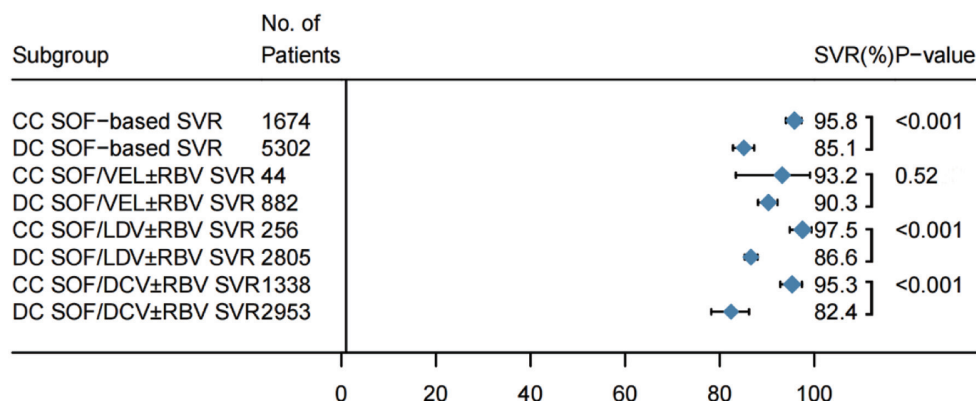
Fig. 3. Treatment outcomes of patients with compensated versus decompensated cirrhosis. Horizontal bars are 95% confidence intervals (CIs) The box size indicates relative sample size. Two-tailed *p*-values <0.05 are significant (meta-regression).

CI: 85.3–88.0) vs. 97.5% (95% CI: 94.8–99.4); *p*<0.001)] (Supplementary Fig. 2), or SOF/DCL±RBV [82.4% (95% CI: 78.2–86.2) vs. 95.3% (95% CI: 92.8–97.4); *p*<0.001)] (Supplementary Fig. 3). When compared with patients with compensated cirrhosis, decompensated cirrhotic patients had a significantly lower pooled SVR rate [10.14% (95% CI: 5.8–16.4) with SOF/LDV±RBV and 12.0% (95% CI: 6.7–17.2)] with SOF/DCV±RBV. The combined SVR rates were similar in both groups (compensated vs. decompensated) when patients received SOF/VEL±RBV [93.2% (95% CI: 83.4–99.1) vs. 90.3% (95% CI: 88.1–92.2); *p*=0.52)] (Supplementary Fig. 4).

Subgroup SVR analysis by DAA regimens in decompensated patients

Further analysis with stratification by DAA regimen indicated that SOF/VEL±RBV had a significantly higher SVR12 rate than those of other regimens in decompensated cirrhotic patients. Nineteen of the 33 studies included a total of 2,805 patients with decompensated cirrhosis who were treated with SOF/LDV±RBV. Nineteen included 1,615 with decompensated cirrhosis and treated with SOF/DCV±RBV, and eight included 882 patients with decompensated cirrhosis treated with SOF/VEL±RBV. The pooled SVR rates (Fig. 4) of HCV patients decompensated cirrhosis treated with SOF/VEL±RBV was 91.0% (95% CI: 87.7–93.9), which was significantly higher than that of patients treated with SOF/LDV±RBV [(86.3% (95% CI: 84.6–87.8)] or SOF/DCV±RBV [82.4% (95% CI: 78.2–86.2)] (Supple-

mentary Fig. 5). In the meta-regression model, patients treated with SOF/VEL±RBV had 8.3% (95% CI: 2.1–14.5) and 6.4% (95% CI: 3.2–9.8) higher SVR rates than patients treated with SOF/DCV±RBV and SOF/LDV±RBV, respectively.

The impact of ribavirin on SVR in decompensated patients

To analyze the effect of ribavirin on treatment outcomes in HCV patients with decompensated cirrhosis, we compared the pooled SVR rates of 1,010 who received SOF-based DAA without RBV and 1,658 with RBV. In the meta-regression analysis (Fig. 5), the SVR rates in patients treated with RBV [83.8% (95% CI: 76.8–89.8)] and without RBV [84.9% (95% CI: 81.7–87.9)]; were not significantly different (*p*=0.76) (Supplementary Fig. 6). Subgroup analysis of different DAA regimens found that at both 12 versus 24 weeks of treatment, the effectiveness of achieving SVR was similar with or without use of RBV. The pooled data indicated that when the three regimens (SOF/LDV, SOF/DV, or SOF/VEL) were compared, differences in the enhancement of the SVR rate with the addition RBV to each therapy after 12 or 24 weeks of treatment were not significant. All regimens had similar pooled SVRs in this special population. Among those who received SOF/VEL, adding RBV (*n*=170) did not significantly increase the SVR rate compared with the patients (*n*=449) treated without RBV [90.0% (95% CI: 80.3–96.8) vs. 91.5% (95% CI: 86.5–95.5); *p*=0.70] (Supplementary Fig. 7).
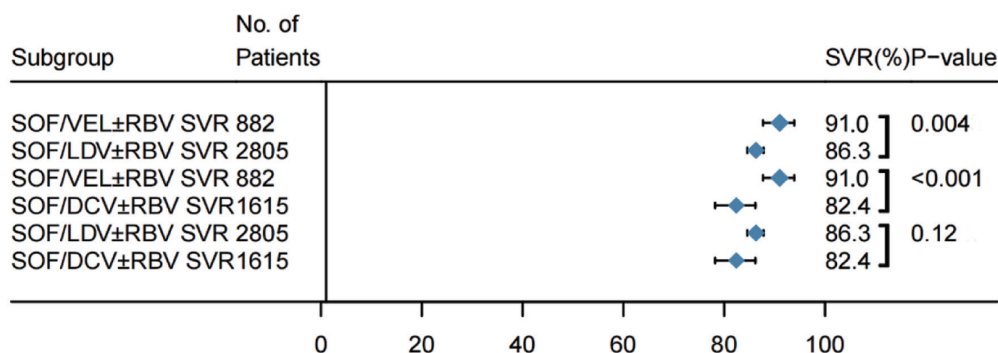

Fig. 4. SVR12 rates of patients with decompensated cirrhosis on different regimens. Horizontal bars are 95% confidence intervals (CIs); box size indicates relative sample size. (*n*=36). Two-tailed *p*-values <0.05 are significant (meta-regression).
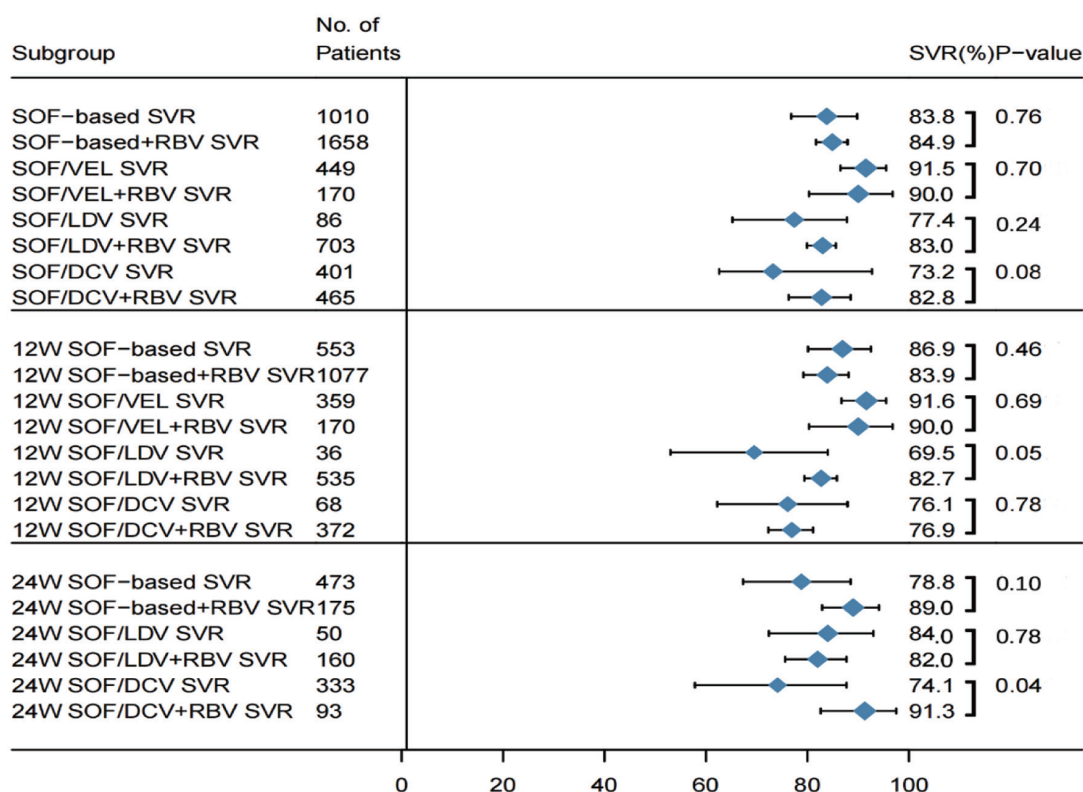
Fig. 5. Outcomes of decompensated patients treated with and without RBV. Horizontal bars are 95% confidence intervals (CIs); box size indicates relative sample size. (*n*=36). Two-tailed *p*-values <0.05 are significant (meta-regression).

Overall safety outcomes of DAA therapy in decompensated patients

Of the 33 studies reviewed, 8/33, 15/33, 7/33, and 16/33 studies that reported safety data in terms of AEs, SAEs, HCC, and case-fatality in the total of 1,141, 2,547, 1,433, and 2,832 study patients, respectively (Fig. 6). The overall heterogeneity across the studies of the four safety outcomes was high, with an I^2 of >50% for each assessment. A random-effect model was used for the analysis of AEs, SAEs, HCC, and case-fatality across the studies. The compiled percentage of the AEs (i.e. one or more AE including headache, dizziness, nausea, vomiting, diarrhea, and the others reported by the investigators) was 69.0% (95% CI: 48.6–86.2). In addition, the percentage of patients who discontinued DAA treatment because of AEs (Supplementary Table 4) was 3.2% (95% CI: 1.5–5.2). The pooled percentage of SAEs, naïve in the onset of acute myocardial infarction, chronic obstructive pulmonary disease, epilepsy, mania, and others, was 16.2% (95% CI: 10.8–22.4). The pooled percentage of HCC was 3.1% (95% CI: 1.5–5.0) and that of death was 4.6% (95% CI: 3.1–6.3) in decompensated patients who received DAA therapy, respectively (Fig. 6).

In patients who were treated with SOF/VEL±RBV, the reported percentages of AEs, SAEs, HCC, and mortality were 64.2% (95% CI: 34.0–89.4), 16.2% (95% CI: 7.5–27.3), 2.9% (95% CI: 0.4–7.3), and 3.8% (95% CI: 1.7–6.5); respectively (Supplementary Fig. 8). In patients treated with SOF/DCV±RBV, the percentages of AEs, SAEs, HCC, and mortality were 62.1% (95% CI: 39.1–82.6), 15.9% (95% CI: 8.0–25.7), 2.9% (95% CI: 0.1–8.7), and 6.7% (95% CI: 3.9–10.1); respectively. Lastly, the percentages

of AEs, SAEs, HCC, and mortality in patients treated with SOF/LDV±RBV were 77.5% (95% CI: 27.9–100), 20.3% (95% CI: 3.6–45.7), 3.6% (95% CI: 0.7–8.2), and 3.8% (95% CI: 1.7–6.6); respectively.

Safety profiles of DAAs in decompensated versus compensated patients

The difference in incidence of AEs in decompensated and compensated patients treated with DAAs [69.0% (95% CI: 48.6–86.2) vs. 70.8% (95% CI: (30.7–97.8); *p*=0.93)] was not significant. However, patients with decompensated cirrhosis had a significantly higher frequency of SAEs [2% (95% CI: 10.8–22.4) vs. 2.8% (95% CI: 0.9–5.7%); *p*<0.001], incidence of HCC [3.1% (95% CI: 1.5–5.0) vs. 0.0% (95% CI: 0.0–0.9); *p*=0.001]; and case-fatality rate [4.6% (95% CI: 3.1–6.3) vs. 0.5% (95% CI: 0.2–0.); *p*<0.001) on DAA therapy (Supplementary Figs. 9–11, and Supplementary Table 5).

Safety analysis in decompensated patients treated with or without RBV

To gain a better understanding of the safety profile in decompensated patients treated with regimens containing RBV, we compared the pooled safety data with those of patients on DAA therapy without RBV (Fig. 7). Patients who were treated with RBV (*n*=723) had a significantly higher frequency of AEs [89.2% (95% CI: 68.1–99.9) vs. 52.9% (95% CI: 28.0–77.7); *p*=0.03] (Supplementary Fig. 12), compared with those without RBV treatment (*n*=418). The
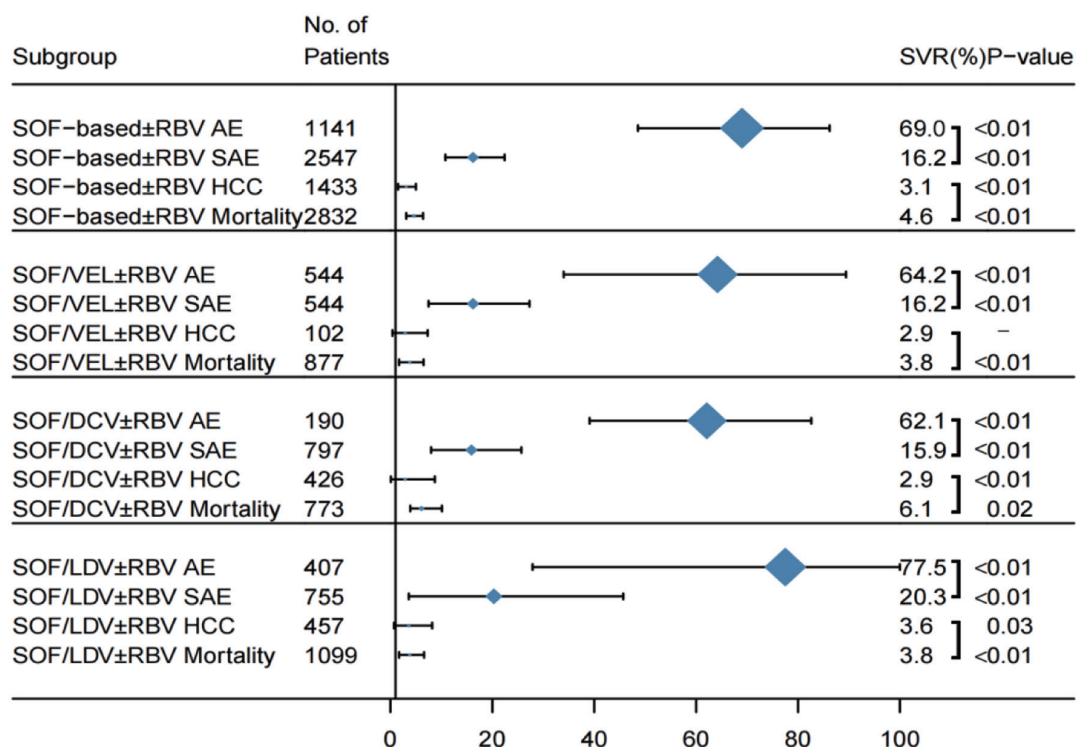
Fig. 6. Pooled safety results of patients with decompensated cirrhosis. Dotted vertical line and diamond show the summary effect (random-effect model); outer edge shows 95% confidence intervals (CIs). AEs, adverse reactions; SAEs, serious adverse reactions; HCC, hepatocellular carcinoma.

frequency of SAEs in patients treated with RBV (*n*=721) was also significantly higher than that of patients (*n*=681) who were given DAAs without RBV [24.9% (95% CI: 16.3–34.7) vs. 12.8% (95% CI: 7.5–19.1); *p*=0.03] (Supplementary Fig. 13). In the meta-regression analysis, the frequencies of AEs and SAEs in patients treated with RBV increased by 33.3% (95% CI: 8.9–57.8) and 11.1% (95% CI: 1.7–23.9), respectively. The adverse effects associated with adding RBV and extending treatment duration are shown in Supplementary Table 5. There were no significant differences (*p*>0.05) in the frequencies of HCC and case-fatality rates between the two treatment methods (Fig. 8). In patients treated with SOF/VEL (Supplementary Fig. 14), the frequency of AEs was significantly higher in those with RBV than in those without RBV [50.2% (95% CI: 18.9–81.4) vs. 91.1% (95% CI: 85.4–95.6); *p*=0.008). The results are consistent with the overall safety profile for patients with RBV treatment.

Publication bias

A sensitivity analysis of the effect on the overall results by excluding individual studies showed that the pooled SVR was not significantly changed by exclusion of any one of the 33 studies, indicating the robustness of the current analysis. Egger's funnel plots (Supplementary Fig. 15) showed that the meta-analysis had no significant publication bias (*p*=0.83) as the plot of the included studies was symmetrical (Supplementary Fig. 16).

Discussion

SOF-based regimens are recommended by AASLD-IDSA and EASL guidelines for the treatment of decompensated cirrhotic patients with HCV. Both guidelines suggest SOF/VEL+RBV for
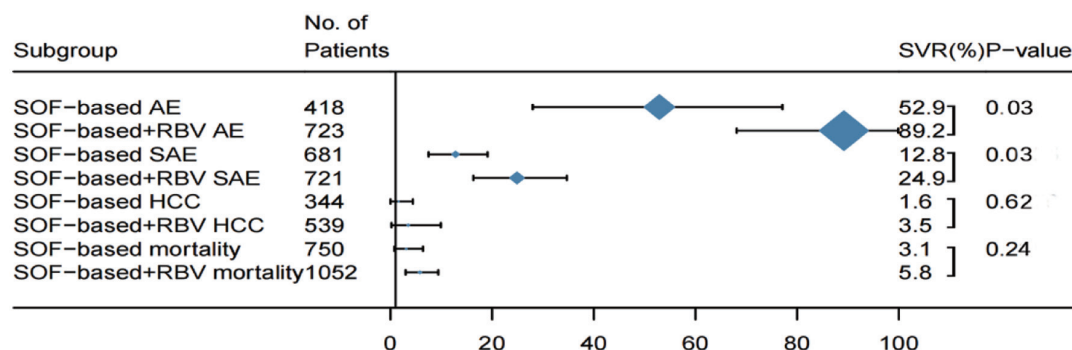

Fig. 7. Safety profiles for decompensated patients treated with and without RBV. Horizontal bars are 95% confidence intervals (CIs); box size indicates relative sample size. (*n*=36). Two-tailed *p*-values <0.05 are significant (meta-regression).
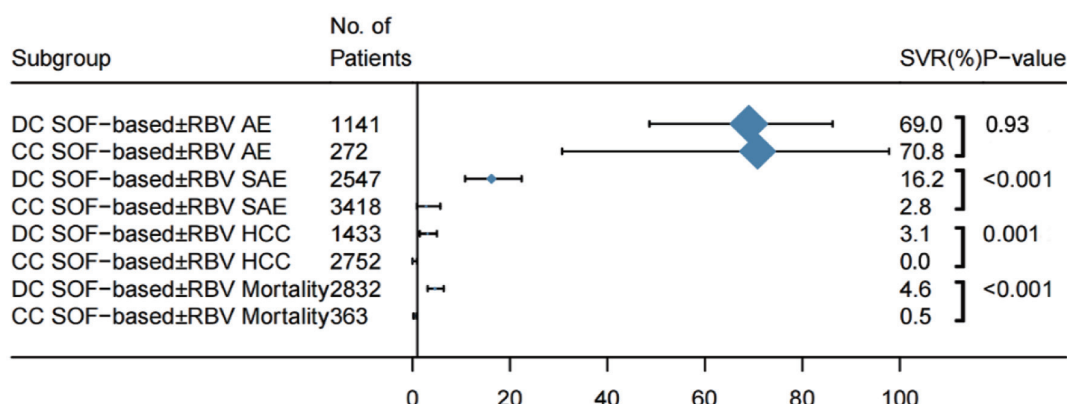
Fig. 8. Safety profiles for decompensated and compensated patients treated with and without RBV. Horizontal bars are 95% confidence intervals (CIs); box size indicates relative sample size. (*n*=36). Two-tailed *p*-values <0.05 are significant (meta-regression).

12 weeks (preferred) or SOF/VEL without RBV for 24 weeks (for RBV contraindications or poor tolerance) for decompensated patients. In addition, the AASLD and IDSA guidelines also recommend SOF/LDV+RBV for 12 weeks (preferred) or SOF/VEL without RBV for 24 weeks (for RBV contraindications or poor tolerance). The recommendations are based on the findings of a few pivotal or cohort studies including SOLAR-1, SOLAR-2, ASTRAL-4, and HCV-TARGET, and the US chorionic hepatitis cohort study.[8,41,42,51] However, the meta-analysis data was not available when the guidelines were published.

To the best of our knowledge, this study including 33 RCTs or cohort study data is the first meta-analysis for HCV patients with decompensated cirrhosis. We found that SOF-based regimes in patients with decompensated cirrhosis had a 10.1% (95% CI: 6.6–13.6) points lower pooled SVR rate than that in patients with compensated disease. However, SVR rates in the two groups (compensated vs. decompensated) were similar when patients received SOF/VEL±RBV therapy (93.2% vs. 90.3%; *p*=0.52), which suggests that decompensated status did not negatively impact the SVR achieved with the SOF/VEL regimen. A subgroup analyses confirmed that SOF/VEL±RBV therapy had a significantly higher SVR rate (91.0) for decompensated cirrhotic patients compared with SOF/LDV±RBV regimens (86.3%, *p*=0.004), or SOF/DCV±RBV (82.4%, *p*<0.001). The findings further support SOF/VEL±RBV as the first-line treatment in this subpopulation. Our study provides new evidence to address the discrepancy between the EASL and AASLD-IDSA guidelines for the use of SOF/LDV±RBV for decompensated patients. Most important, the current meta-analysis demonstrated that adding RBV to SOF/LDV or SOF/VEL regimens failed to improve the pooled SVRs, but RBV increased the frequency and severity of AEs. Pooled data pointed in the direction of using 12 weeks of SOF/VEL for decompensated patients without RBV as the optimal regimen. The pooled SVR of 359 patients was 91.6. Lastly, our meta-analysis showed that decompensated patients on DAAs had a higher frequency of SAEs, incidence of HCC, and case-fatality rate compared with those of compensated patients. The findings further support the guideline approaches of close monitoring during the DAA treatment. In patients who could not tolerate VEL for HCV treatment, the alternative might be SOF/LDV without ribavirin for 12 weeks or SOF/DCV with ribavirin for 24 weeks.

Several study limitations should be discussed. The meta-analysis did not include the study by Lu *et al*.[52] that was cited by EASL guidelines to support the use of RBV combined with the SOF/VEL regimen. In that study, the odds ratio of SVR in decompensated patients who received SOF/VEL with RBV (*n*=1,135) and without RBV (*n*=2,996) were 0.48 (95%

CI: 0.27–0.86) and 0.13 (95% CI: 0.07–0.24), respectively. We did not include Lu *et al*.[52] in this meta-analysis because it did not report the number of patients who achieved a SVR in the regimen we studied, which met the exclusion criteria of our study. In their study, patient data were compiled together including the first, second, and the third generation of DAA treatment for decompensated cirrhotic patients and the use of RBV was associated with higher SVR in a multivariate model.[52] Although the current analysis did not show the enhancement of SVR when adding RBV to genotype 3 patients with liver decompensation, the number of patients in comparison was limited to less than 70 patients. Further meta-analysis is needed to confirm these findings when more genotype 3 studies are available. Another general concern for a meta-analysis is the significant heterogeneity of studies included in the meta-analysis. To minimize such impact on the analysis, we had performed comparisons of SVRs for the subgroups including 12-week therapy vs. 24-week therapy, Asian vs. non-Asian patients, and RCT vs. non-RCT studies. Based on the subgroup analyses, there were no heterogeneity sources in our study. Furthermore, the majority of published studies were non-RCTs. We did not assess pooled data for RCTs because two RCTs used the SOF/VEL±RBV regimen and had relatively small sample sizes. Other possible selection biases inherit in a meta-analysis design included data from studies in different practice settings, patient enrollment criteria, or baseline values at enrollment. Finally, most of the studies were uncontrolled single-arm studies, which limited the ability to draw firm conclusions about the safety and effectiveness of the protocol. Despite the above limitations, the strength of our meta-analysis lies in its exhaustive literature research, well-defined approach for data selection and extraction, comprehensive statistical analyses, reporting in accord with PRISMA statements, and no significant evidence of publication bias.

In conclusion, our meta-analysis showed that SOF/VEL±RBV regimens had a significantly higher pooled SVR rate (91.0%) for decompensated cirrhotic patients compared with SOF/LDV±RBV (86.3%, *p*=0.004) and SOF/DCV±RBV (82.4% *p*<0.001). In addition, patients treated with SOF/VEL without RBV for 12 weeks achieved an SVR of 91.5%, which was similar to that of SOF/VEL+RBV (90.0). There was no data on SOF/VEL±RBV for 24 weeks, and adding RBV to SOF-based regimens increased the overall frequency of AEs or SAEs, our results suggest that SOF/VEL regimen without RBV was the best option in the clinical setting for HCV patients with liver decompensation when considering the efficacy and the AEs. Our findings have very important clinical implications that may serve as the evidence base for selecting SOF/VEL as the first-line treatment without RBV

and potentially change future guidelines or the standard of clinical practice. SOF/LDV should be avoided because of the inferior efficacy in decompensated patients when compared with SOF/VEL. In patients who must be treated with SOF/LDV (*n*=36), it was not clear whether 24 weeks of therapy had a significantly higher SVR rate than that achieved with 12 weeks of therapy (*n*=50) because of the relatively small sample size. However, adding RBV had no significant impact on the SVR with either 12 or 24 weeks of SOF/LDV therapy. Our analysis also highlighted the need for future studies in decompensated patients who failed SOF/VEL (about 10) as the SVR rates were significantly lower in decompensated patients than in noncirrhotic patients.

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Conflict of interest

CQP is a speaker and consultant for Gilead Sciences. He also received a research grant from Gilead Sciences and Assembly Biosciences. The other authors have no conflict of interests related to this publication.

Author contributions

Contributed equally to this work (WZ, JZ, ST), involved in data extraction, data analysis, drawing, and article proofreading (WZ), involved in all stages of the review and supervised the conduct of the study (JZ), drafted the first draft and wrote the manuscript (ST), searched and filtered the literature (YL, XD), extracted data (LQ, ML), participated in analysis planning, interpretation of the data, and writing the manuscript, performed a critical review of the manuscript, and addressed the comments of the journal reviewers (CQP), and conceptualized the topic, supervised and facilitated the conduct of the study (HY). All authors reviewed and approved the final version of the manuscript.

Data sharing statement

All data are available upon request

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